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8EHQ-1293-1279

CHEMICAL MANUFACTURERS ASSOCIATION

December 14, 1993

Contains No CBI

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RECD
OFFICE OF POLLUTION
PREVENTION AND TOXICS

Document Processing Officer IMD-7407
Attention: 8(e) Coordinator
Information Management Division
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460

8EHQ-93-12794
INIT 12/20/93

88940000079

RE: Notice Under TSCA Section 8

Dear Sir/Madam:

The Chemical Manufacturers Association submits this notice in accordance with Section 8(e) of the Toxic Substance Control Act (TSCA) and EPA's 1991 Section 8(e) Reporting Guide. This notice is based on preliminary data from a hrpt mutation frequency study of ethylene oxide (EO), CAS number 75-21-8. CMA is submitting this report on behalf of the Olefins Panel. A list of Panel members is provided in Exhibit I.

Rats and mice were exposed by inhalation to 0 or 200 ppm EO for 6 hours per day, 5 days per week for 4 weeks. Rats were necropsied 5 weeks post-exposure and mice were necropsied 8 weeks post-exposure. Under these conditions, EO produced a 5.6- and 5.0-fold increase in mutation frequency at the hprt gene of isolated splenic T-lymphocytes in rats and mice, respectively, as compared to air-exposed controls. An abstract of the preliminary study results is attached as Exhibit II. The final report will be sent to you when it is received.

The fact that exposure to EO results in an increase in hprt mutations in rodents is not new information. This finding has been reported previously in mice exposed to EO by the i.p. route of administration but not in the rat by any route of administration. Based on the U.S. EPA 1991 Section 8(e) Reporting Guide, the findings discussed above appear to be reportable under TSCA Section 8(e).

If you have any questions, please call me at 202/887-1182.

Sincerely,

RECEIVED
1-11-94

Elizabeth J. Moran, Ph.D.
Manager, Olefins Panel

2501 M Street, NW, Washington, DC 20037 Telephone 202-887-1100 Fax 202-887-1237

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A Public Commitment

3 pgs.

EXHIBIT I

MEMBERS OF THE OLEFINS PANEL

Amoco Chemical Company
Asahi Chemical Industry America, Inc.
Chevron Chemical Company
Dow Chemical Company
DuPont
Eastman Chemical Company
Exxon Chemical Company
Fina Oil and Chemical Company
Lyondell Petrochemical Company
Mobil Chemical Company
Novacor Chemicals Ltd.
Oxy Petrochemicals,Inc
Quantum Chemical Corporation
Phillips Petroleum Company
Shell Oil Company
Texaco Chemical Company
Union Carbide Corporation
Union Texas Products Corporation

Exhibit II

"Risk Assessment in Environmental Carcinogenesis"

Biomarkers As Potential Quantitative Indicators of the In Vivo Metabolism of Ethylene to Ethylene Oxide. Vernon E. Walker, Myung H. Cho, Patricia B. Upton, Nova A. Scheller, Thomas R. Skopek, and James A. Swenberg, University of North Carolina, Chapel Hill, NC 27599.

Although no concentration-related increases in the incidence of tumors have been observed in cancer bioassays with ethylene, some questions remain concerning ethylene's carcinogenic potential. These concerns are based upon several studies which have shown that ethylene from both endogenous and exogenous sources is metabolized to ethylene oxide (ETO) in rats, mice, and humans (see *Mutation Res. 233:* 151, 1990). In contrast to ethylene, ETO has been demonstrated to be carcinogenic in mice and rats chronically exposed to high concentrations of this agent. ETO can react with cellular macromolecules including DNA and protein and has been shown to be mutagenic in a variety of assays. Identical DNA and protein reaction products have been observed after exposure of mice to ethylene and have been attributed to its metabolism to ETO. The calculated risk of cancer from ethylene exposure is based on the premise that a linear relationship exists between ETO exposure and tumor induction. This relationship is only valid if linear relationships also exist between ETO exposure and the induction of critical cellular events involved in tumorigenesis. To investigate this relationship, intracellular dosimeters of exposure and effect must be identified and quantitated for both ETO and ethylene.

The purpose of the present study is (i) to investigate the potential use of several biomarkers as quantitative indicators of the *in vivo* conversion of ethylene to ETO and (ii) to generate molecular dosimetry data that may improve risk assessment for humans exposed to ethylene or ethylene oxide. To this end, male F344 rats and B6C3F1 mice (7 weeks old) were exposed by inhalation to 0 or 3000 ppm ethylene for 1, 2, or 4 weeks (6 hr/day, 5 days/week) or to 0, 40, and 1000 ppm ethylene for 4 weeks. Additional animals were exposed to 200 ppm ETO for 4 weeks to provide positive controls. Hemoglobin adducts [N-(2-hydroxyethyl)valine; HEVal], DNA adducts [7-(2-hydroxyethyl)guanine; 7-HEG], abasic sites, and mutation frequencies at the *hprt* gene are being assessed as potential biomarkers for determining the molecular dose of ETO resulting from ethylene metabolism in exposed rats and mice. HEVal is being quantitated by Edman degradation and GC-MS, 7-HEG is being measured by a new GC-MS method, AP sites are being quantified by a new assay based on the "aldehyde reactive probe" reagent (*Biochemistry 31:* 3703, 1992) and immuno-slot-blot, and *hprt* mutation frequencies are being defined according to Skopek et al. (*PNAS 89:* 7866, 1992). Preliminary data are available for hemoglobin adducts and *hprt* mutations in exposed rats, and for *hprt* mutations in exposed mice. Repeated exposures of rats to 3000 ppm ethylene led to accumulation of HEVal [with initial measurements (n=5-7) giving 1.4, 2.6, and 5.6 pmol adduct/mg globin after 1, 2, and 4 weeks exposure, respectively]. The dose response curve for HEVal was non-linear in rats exposed to ethylene for 4 weeks [with initial measurements (n=5-7) giving 1.3, 5.3, and 5.6 pmol adduct/mg globin at 40, 1000, and 3000 ppm, respectively]. Comparison of this dose response data to that previously obtained in ETO-exposed rats (*Cancer Res. 52:* 4320, 1992) supports the kinetics of ethylene elimination described by Bolt and Filser (*Arch. Toxicol. 60:* 73, 1987). Exposures to 200 ppm ETO for 4 weeks led to *hprt* mutant frequencies in splenic T-lymphocytes that were 5.6- and 5.0-fold above background in rats and mice necropsied 5 and 8 weeks postexposure, respectively; however, no treatment effects were observed in animals (n=6-7/group) exposed to ethylene (40, 1000, or 3000 ppm). The mutant frequencies in control rats and mice were 1.2 ± 0.3 SD x 10^{-6} and 2.0 ± 0.8 SD x 10^{-6}, respectively. These preliminary results suggest that forthcoming data on DNA adducts and abasic sites may be important for understanding the relationships between ethylene metabolism to ETO, exposures to ETO, and the potential for induction of mutations and cancer. (Supported by a grant from the Chemical Manufacturers Association).

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Elizabeth J. Moran, Ph.D.
Manager, Olefins Panel
Chemical Manufacturers Association
2501 M Street, N.W.
Washington, D.C. 20037

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

APR 19 1994

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite this number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure

12794 A

CPCATS/TRIAGE TRACKING DBASE ENTRY FORM

CPCATS DATA
Submission # 12793 - 12794 SEQ A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Chemical Manufacturers Association

SUB DATE: 12/14/93 OTS DATE: 12/20/93 CSB DATE: 01/11/94

INFORMATION REQUESTED FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:

CAS#
75-21-8
74-85-1

INFORMATION TYPE:		P	F	C
0201	ONCO (HUMAN)	01	02	04
0202	ONCO (ANIMAL)	01	02	04
0203	CELL TRANS (IN VITRO)	01	02	04
0204	MUTA (IN VITRO)	01	02	04
0205	MUTA (IN VIVO)	01	02	04
0206	REPRO/TERATO (HUMAN)	01	02	04
0207	REPRO/TERATO (ANIMAL)	01	02	04
0208	NEURO (HUMAN)	01	02	04
0209	NEURO (ANIMAL)	01	02	04
0210	ACUTE TOX. (HUMAN)	01	02	04
0211	CHR. TOX. (HUMAN)	01	02	04
0212	ACUTE TOX. (ANIMAL)	01	02	04
(0213)	SUB ACUTE TOX (ANIMAL)	(01)	02	04
0214	SUB CHRONIC TOX (ANIMAL)	01	02	04
0215	CHRONIC TOX (ANIMAL)	01	02	04

INFORMATION TYPE:		P	F	C
0216	EPI/CLIN	01	02	04
0217	HUMAN EXPOS (PROD CONTAM)	01	02	04
0218	HUMAN EXPOS (ACCIDENTAL)	01	02	04
0219	HUMAN EXPOS (MONITORING)	01	02	04
0220	ECO/AQUA TOX	01	02	04
0221	ENV. OCCC/REL/FATE	01	02	04
0222	EMER INCI OF ENV CONTAM	01	02	04
0223	RESPONSE REQEST DELAY	01	02	04
0224	PROD/COMP/CHEM ID	01	02	04
0225	REPORTING RATIONALE	01	02	04
0226	CONFIDENTIAL	01	02	04
0227	ALLERG (HUMAN)	01	02	04
0228	ALLERG (ANIMAL)	01	02	04
(0239)	METAB/PHARMACO (ANIMAL)	(01)	02	04
0240	METAB/PHARMACO (HUMAN)	01	02	04

INFORMATION TYPE:		P	F	C
0241	IMMUNO (ANIMAL)	01	02	04
0242	IMMUNO (HUMAN)	01	02	04
0243	CHEM/PHYS PROP	01	02	04
0244	CLASTO (IN VITRO)	01	02	04
0245	CLASTO (ANIMAL)	01	02	04
0246	CLASTO (HUMAN)	01	02	04
(0247)	DNA DAM/REPAIR	01	02	04
0248	PROD/USE/PROC	01	02	04
0251	MSDS	01	02	04
0299	OTHER	01	02	04

TRIAGE DATA:

NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION
YES (CONTINUE)	YES (DROP/REFER)	RAT	LOW		
NO (DROP)	NO (CONTINUE)	MUS	(MED)		
INSUFFICIENT	REFER		HIGH		

COMMENTS: [illegible]

12) 8EHQ-1293-12794: Rank - medium.

Chemical: Ethylene oxide (EO: CAS# 75-21-8).

Biomarkers as Potential Quantitative Indicators of the In Vivo Metabolism of Ethylene to Ethylene Oxide, V.E., Walker et al., "Risk Assessment in Environmental Carcinogenesis", accompanying letter from CMA, Washington, DC, dated December 14, 1993: Positive for gene mutations at the hprt locus in the spleens of rats and mice exposed in vivo by inhalation.